Exhibit 3

Katherine Keyes expert witness report

I. Background and Qualifications

A. Summary

I am an Associate Professor of Epidemiology at Columbia University, specializing in substance use and substance use disorders epidemiology.

B. Education

I received a Masters degree in Public Health from Columbia University in 2004, and a PhD in Epidemiology from Columbia University in 2010.

C. Field of specialty and employment history

My field of specialty is substance use and substance use disorders, as well as related comorbidity, focusing on psychiatric disorders, and consequences of substance use including intentional and unintentional injury. After receiving my PhD in Epidemiology in 2010, I completed a post-doctoral fellowship in Epidemiology at Columbia University from 2010 through 2012, and then was recruited by Columbia University to join the faculty in 2012 as a tenure-track Assistant Professor. I was promoted to Associate Professor in 2016. I also hold academic appointments at various other universities. I am a Research Assistant Professor at the University of Michigan, and an Adjunct Associate Professor at the Society for Health and Research at Universidad Mayor in Santiago, Chile.

D. Research areas and publications

I have published 225 peer-reviewed articles and book chapters, more than 60 of which are first-authored. Much of this research has been published in the leading, highest impact epidemiology, psychiatry, and substance use journals, including in *Pediatrics, JAMA Psychiatry, Lancet Psychiatry, Nature Communications, British Medical Journal, British Journal of Psychiatry, American Journal of Psychiatry, American Journal of Epidemiology,* and *International Journal of Epidemiology*, among others. My articles have been cited in numerous disciplines, including psychiatry, epidemiology, public health, and pediatrics. My *h*-index ranges from 43 (Web of Science) to 60 (Google Scholar)[1]. Currently, 50 of my articles have been cited more than 100 times; 15 of my articles have been cited more than 200 times; and 4 have been cited more than 500 times. Since obtaining my doctoral degree, I have led numerous and sustained extramurally funded grants as Principal Investigator, and have successfully competed for grant funding from the National Institutes of Health to conduct my research. I have received numerous grants from Columbia University for my work, including the Calderone Prize for junior faculty, and the Tow scholarship (awarded to high-achieving mid-career scientists). I serve as a co-Investigator on numerous federally-funded grants both at Columbia and at other institutions (including University of Michigan and New York University).

I have published two textbooks on epidemiological methods, and I am well-qualified to assess the literature on opioid-related harm. The first is *Epidemiology Matters: A New Introduction to Methodological Foundations*, published by Oxford University Press in 2014, which is currently being used to teach graduate students about epidemiological methods in more than 20 universities. The second is *Population Health Science*, also published

[1] An h-index is a measure of productivity and research impact. It is the median level of correlation between number of peer-reviewed papers and the number of times each paper has been cited for a given scholar. As such, an h-index of 60 indicates that I have published a median of 60 papers that have been cited at least 60 times. Benchmarks for h-indices vary; at Columbia University department of epidemiology, the standards for promotion are an h-index of at least 15 for promotion to Associate Professor, and at least 25 for promotion to professor. My h-index is more than twice that needed for a full professor rank in my department at Columbia University, indicative of high productivity and impact.

greater than heroin and synthetic opioids combined over the course of the epidemic, and that the burden is not substantially decreasing, underscoring the public health burden of prescription opioid overdose.

The empirical literature demonstrates an association between the opioid supply and the increase in prescription opioid deaths. Based on retail pharmacy data in two provinces in Canada from 2005 through 2009, Fisher et al. (2013) documented statistically significant and high correlations between the rate of hydromorphone dispensing and deaths due to hydromorphone, as well as the rate of oxycodone dispensing and deaths due to oxycodone. These correlations were high within-province, which is important because the base rates of overdose and dispensing varied by province and yet the correlations remained strong in each. Similar associations with non-fatal outcomes such as substance abuse treatment admissions have been published by the same investigators, indicating that the association between prescription opioid supply and opioid-related harms in Canada extends across outcomes related to opioid use disorder as well as opioid overdose.[65]

In the United States, Paulozzi & Ryan (2006),[66] documented wide variation across US states in the distribution of prescription opioids, based on data from the Automated Reports and Consolidated Orders System (ARCOS). Scholars estimated the total rate of prescription opioid dispensing per 100,000 in each state in 2002, and correlated it across states with the drug poisoning death rate per 100,000 based on vital statistics data. Two findings are noteworthy. First, there was wide variation in opioid prescribing across states. For example, hydrocodone distributions ranged over 12-fold across states, and oxycodone distributions ranged over 7-fold; such variations are noteworthy because to my knowledge there is not sufficient data to conclude that the pain need for such medications varies by 7 to 12-fold across US states. Further, this variation across states was highly correlated with drug poisoning rates; all prescription opioids combined were correlated with drug poisoning deaths at 0.73 for the correlation coefficient, which indicates a high correlation. Investigators reported the total amount of variation, that is, differences between state-level overdose rates and the national average, that was explained by each drug. Note that variance explained is not the same as the risk of overdose, or the proportion of overdose deaths due to a particular drug, rather, it is another way to express correlation. Oxycodone dispensing alone explained 43% of the variation in drug poisoning mortality; methadone dispensing explained 46%. While the death rates from methadone substantially contributed to mortality variation in Paulozzi & Ryan (2006), it should be noted that death rates from methadone have declined precipitously since the time period of the study. Methadone death in the US reached a height in 2006/2007 at 1.8 per 100,000, and had declined annually since then, stabilizing at 1.0 per 100,001 in 2015-2017, [64] which is a 44% decerase in just one decade. Methadone now contributes a relatively small proportion of drug overdose events, with most recent data suggesting that 14.7% of overdose deaths are attrituable to methadone. These declines are attributable to Food and Drug Administration warnings and guidelines for methadone prescribing, as well as voluntary limits on the distribution of high milligram formulations of methadone among manufacturers.[67] Given the declines in methadone use, the findings on methadone in Paulozzi & Ryan (2006) regarding the proportion of variance explained in geographical death rates do not generalize to distributions of opioid related harm in recent years. However, prescription opioid overdose deaths are higher than methadone rates of death and have remained relatively stable in recent years, suggesting that geographic variation explained in prescription opioid overdose deaths is more generalizable than methadone death rates.

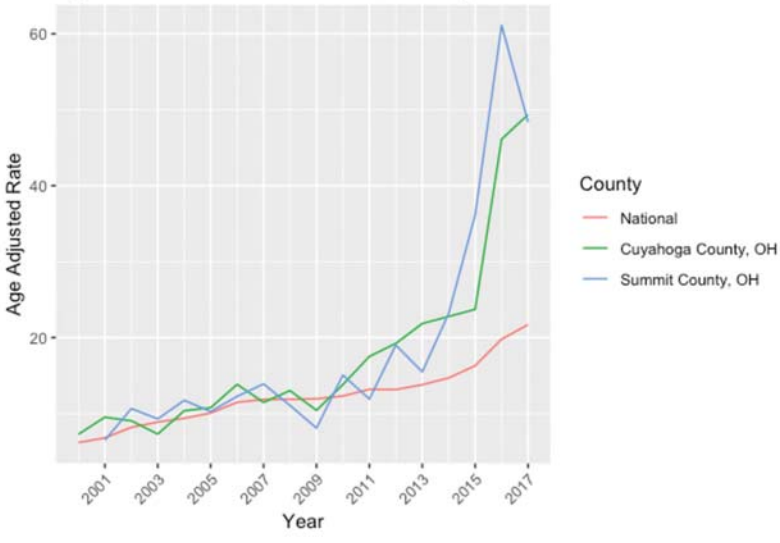
Further, Wisniewski et al. (2008)[68] examined the relationship between prescribing of opioids and non-medical opioid use, as well as emergency department visits related to opioids. Data on prescribing were drawn from the National Hospital Ambulatory Medical Care Survey and the National Ambulatory Medical Care Survey; opioid prescriptions were based on medication codes indicating whether hydrocodone, oxycodone, or a morphine-containing product were prescribed at each patient encounter (including 576,178 patient encounters). Prescription rates increased from 2-fold for hydrocodone, 2.64 for morphine, and 3.21 for oxycodone products from 1995 to 2004. Concomitantly, opioid-related emergency department visits based on DAWN data and respondent reports of non-medical opioid use based on NSDUH data increased across the same time period. Correlations between rates of prescription and rates of opioid-related ED visits and non-medical use were significant for hydrocodone (correlations ranged between 0.73 to 0.79) and oxycodone

(correlations ranged from 0.76 to 0.87). Taken together, these data indicate strong and statistically significant correlations between opioid supply and prescribing practices, and opioid-related harm in the US population.

Pharmaceutical company marketing to physicians, often based on sources that underestimated the risk of opioid use disorder, harm, and diversion, as discussed in Section B.2., contributed to the increase in the supply of opioids.[15] These marketing practices led to consequences for opioid-related harm. Pharmacuetical company marketing to physicans is extensive in the United States.[17] Empirical evidence has demonstrated that industry payments to physicians as part of the marketing of prescription opioids were associated with increased opioid prescriptions,[69] and that 1 in 12 physicians in the US, and 1 in 5 family physicians, received opioid-related marketing.[17,69–71] Hadland et al. (2019)[72] used data form the Centers for Medicare & Medicaid Service Open Payments database to assess the monetary value in payments to physicians for opioid products in all US counties over time, as well as data on dispensing of opioids in available counties in the US, and examined the spatial and temporal correlations with prescription opioid deaths as designed in the vital statistics records. Authors used a rigorous statistical model that included controls for a range of county-level factors such as economic environment (e.g. unemployment, income, income inequality) as well as demographics. Results demonstrated that even with statistical controls in place, each one standard deviation increase in payments to physicians was associated with statistically significant increases in prescription opioid overdose; including when marketing was assessed by marketing value in dollars per capita (each standard deviation increase associated with 1.09 times the rate of death), number of payments to physicians per capita (each standard deviation increase associated with 1.18 times the rate of death), and number of physicians receiving marketing per capita (each standard deviation increase associated with 1.12 times the rate of death). Further, these authors conducted mediation analysis to quantitatively demonstrate that the association between marketing to physicians and prescription opioid overdose was mediated by (that is, explained by) the increase in opioid prescribing and increased distribution. However, it is important to note that payments to physicians are only one type of promotional activity, and accounted for only a proportion of the overall promotion strategy for opioid pharmacueticals. These results are highly rigorous and clearly demonstrate harm to the population from opioid marketing and distribution.

Finally, a working paper authored by Powell et al. (2015)[73] examined the introduction of the Medicare Prescription Drug Benefit (Part D) program in 2006 as a potential driver of the opioid supply among those aged 65+. This paper is particularly relevant given the quasi-experimental design of using an exposure with exogenous variation, and a new law passed heterogeneously across states, to assess changes in the opioid supply. "Exogenous variation" is a term that is commonly used in epidemiological and economics literature to mean that there is no possibility that confounding factors such as increased prevalence of pain, or increased risk factors for addiction, could explain changes in the exposure. Thus, changes in the Medicare system cannot be caused by users of that system, and as such, associations between changes in the Medicare system and changes in opioid supply are more likely to be causal. Using data from 1999 through 2016, authors documented that the Medicare expansion affected the opioid supply, with states that had a relatively larger proportion of individuals gaining access to prescription drug coverage exhibiting an increase in opioid supply based on ARCOS data. Further, authors examined correlations with drug overdose deaths, and specifically those with codes that indicate prescription opioid poisoning, as well as substance abuse treatment admissions, an indicator of the occurrence of opioid use disorders. For both prescription deaths and treatment admissions, there was evidence that the increase in the opioid supply was associated with increases in deaths and treatment admissions; results were robust to a range of sensitivity analyses, alternative modeling of the statistical associations, and a range of quasi-experimental statistical models. As such, these data reinforce the conclusion that the opioid supply directly affects opioid-related harm, and provide a strong design and test of the hypothesis using the quasi-experimental instrument of changes in Medicare prescription coverage.

Figure 3. Overdose death rates, all drugs



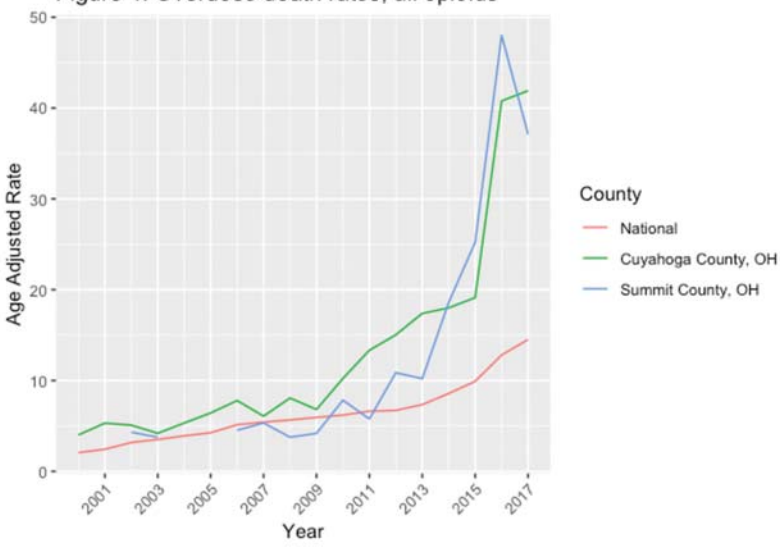
ICD-Codes: Underlying Cause: X40-X44, X60-X64, X85, Y10-Y14, Contributing Cause: T36-T50

In summary, the available evidence, including temporal and geographic covariance of opioid supply as well as quasi-experimental changes in opioid availability, strongly correlate with rates of prescription opioid overdose, providing an evidence base to demonstrate that supply and availability of opioids caused an increase in the rate of prescription opioid overdose.

B.5.1. Opioid-related harm in bellwether counties (Cuyahoga County and Summit counties) has increased greatly between 2000 and the present, and the death rates due to prescription opioids consistently exceed the national average.

The National Vital Statistics Surveillance System publicly provides county-level data on death, allowing for a quantification of the risk of overdose death. Of particular relevance are trends in opioid-related deaths in Cuyahoga and Summit counties. The death rates from 2000 through 2017 for: drug-related death, opioid-related death, and prescription opioid death from the vital statistics records are shown in Figure 3, Figure 4, and Figure 5. Vital statistics has not yet released rates of drug overdose by county for 2018 and 2019, thus we focus on conclusions through 2017 using the data that has been adjudicated and harmonized through the vital statistics process. However, we report on preliminary data from the counties regarding overdose deaths in 2018 as well, though note that estimates may shift as deaths are harmonized with the vital statistics system.

Figure 4. Overdose death rates, all opioids



ICD-Codes: Underlying Cause: X40-X44, X60-X64, X85, Y10-Y14, Contributing Cause: T40.0-T40.4

These data indicate that rates of overdose death in Cuyahoga and Summit counties have been increasing since 2000. Compared to the national average, pharmaceutical opioid deaths were 1.51 times higher in Cuyahoga County than in the nation as a whole in 2000 (based on 32 deaths in Cuyahoga County); the standardized mortality ratio comparing pharmaceutical opioid deaths in Cuyahoga County to the national average varied across the years from 2000 to 2016, with some years lower than the national average. By 2016, the pharmaceutical opioid death rate in Cuyahoga County was 3.26 times higher than the national average (based on 425 deaths in Cuyahoga County). A recent publication from the medical examiner's office of Cuyahoga County (Gilson et al. 2017)[74] confirms the recent rapid increases in death from opioids within Cuyahoga County; based on the medical examiner data, the total overdose mortality in Cuyahoga County has increased from 250 in 2006 to 608 in 2016. In recent years, heroin and fentanyl deaths have increased more than any other drug cause; with heroin deaths increasing from 184 to